WEST Search History

DATE: Friday, September 27, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=ADJ		
L23	L21 and pulse$	49	L23
L22	L20 same l1	17	L22
L21	L20 and l1	68	L21
L20	L19 same wave	996	L20
L19	duty ratio	7211	L19
L18	duti ratio	0	L18
L17	L15 and (pulsed same wave same cavita$)	4	L17
L16	L15 and (pulsed wave)	1	L16
L15	L13 and (l1 same pulse$)	66	L15
L14	L13 and (l1 same pulse)	63	L14
L13	l2 and pulse	168	L13
L12	(4071225| 4326553| 4391672| 4401131| 4705054| 4736759| 4736760| 4788992| 4854337| 4979994| 5013366| 5038808| 5383484| 5427622| 5533540| 5579792| 5834871| 6016821| 6019852)![pn]	19	L12
L11	(4071225| 4326553| 4391672| 4401131| 4705054| 4736759| 4736760| 4788992| 4854337| 4979994| 5013366| 5038808| 5383484| 5427622| 5533540| 5579792| 5834871| 6016821| 6019852)![pn]	19	L11
L10	L9 and pulse	1	L10
L9	6276370.pn.	1	L9
L8	L7 and clean$	20	L8
L7	L6 and (liquid or fluid)	114	L7
L6	L4 and pulse	281	L6
L5	L4 and ((134/$)!.CCLS.)	1	L5
L4	L1 and (carrier wave)	401	L4
L3	L2 and (pulse same carrier same wave)	1	L3
L2	L1 and ((134/$)!.CCLS.)	1699	L2
L1	ultraso$ or megaso$	89693	L1

END OF SEARCH HISTORY

WEST

End of Result Set

Generate Collection | Print

L16: Entry 1 of 1 File: USPT Apr 9, 2002

DOCUMENT-IDENTIFIER: US 6368553 B1
TITLE: Ultrasonic force differentiation assay

Abstract Text (1):
An ultrasonic energy source is used to provide a variable force for measuring the binding forces between molecular entities and for sensing the presence of an analyte in a test sample. The device includes a surface that has a first binding member attached thereto and one or more particles that have a second binding member attached thereto. A reaction vessel is provided for exposing the surface to the particles whereby, if the first binding member has a binding affinity for the second binding member, a complex is formed between individual first binding members and individual second binding members and the particles thereby become immobilized with respect to the surface. The ultrasonic energy source is positioned for applying a variable ultrasonic force onto the surface, and the position of the particles is monitored as the intensity of the ultrasonic force is varied.

Brief Summary Text (3):
The present invention relates generally to binding assays such as immunoassays and, more specifically, to the use of force generated from an ultrasonic power source to characterize specific binding interactions and to differentiate specific and nonspecific binding interactions in such assays.

Brief Summary Text (16):
Ultrasonic force has used commercially for a wide variety of industrial and medical purposes including imaging, welding, cleaning, and dispersing solids in a liquid medium. In the field of solid phase assays, the use of ultrasonic force has, up until now, been limited to enhancing the reactivity of a solid phase binder (see, for example, Chen et al, "Ultrasound-Accelerated Immunoassay as Exemplified by Enzyme Immunoassay of Choriogonadotropin", Clinical Chemistry, 30, (1984), pp 1446-1451 or Tarcha et al, "Absorption-enhanced Solid-Phase Immunoassay Method Via Water-Swellable Poly(acrylamide)Microparticles" Journal of Immunological Methods, 125 (1989) pp243-249 or dissociating binder-ligand complexes so that the amount of ligand can be measured or so that the binder can be reused (see, for example, U.S. Pat. No. 4,615,984 to Stoker, incorporated herein by reference, and Haga et al, "Effect of Ultrasonic Irradiation on the Dissociation of Antigen-Antibody Complexes. Application to Homogeneous Enzyme Immunoassay", Chem. Pharm. Bull. 35(9) (1987), pp 3822-2830).

Brief Summary Text (22):
It has now been discovered that force generated from an ultrasonic power source can be used in an assay to measure or characterize molecular interactions, such as binding affinities of ligands and receptors. This is done by attaching a binding member to a bead or other particle that can be observed in real time, for example, through a microscope, and then allowing the particle-bound binding member to bind with a surface-bound binding member to form a complex. The presence of complexes on the surface is detected by observing the presence of immobilized particles on the surface. Ultrasonic force is then applied, and the movement or lack of movement of the particles, indicating dissociation or lack of dissociation of the complexes may be observed by microscopy or other methods of detection. Alternatively, the ultrasonic force may be applied at a strength level that is insufficient to separate

binding members from each other (while dislodging particles bound to the surface by nonspecific interactions) and then gradually increased to the point where the surface-bound binding member and the particle-bound binding member separate and the particles become mobile on the surface. By this same method, the binding strength of different compounds can be measured and compared simultaneously by providing a surface having the different binding members attached to spatially distinguishable areas and by observing on which areas of the surface the particles remain bound as the strength of the ultrasonic force is increased. It is also possible to measure the binding strength of different compounds simultaneously by attaching each different compound to a different distinguishable class of particle and then observing which classes of particles remain bound as the strength of the ultrasonic force is increased.

Brief Summary Text (23):
Therefore, in one aspect, a device and method are provided to measure the binding forces of a first binding member with a second binding member. In this embodiment, a surface is provided that has a first binding member attached thereto, and one or more particles are provided that have a second binding member attached thereto. A reaction vessel is provided for exposing the surface to the particles whereby, if the first binding member has a binding affinity for the second binding member, a complex is formed between individual first binding members and individual second binding members and the particles thereby become immobilized with respect to the surface. An ultrasonic force means is operatively disposed with respect to the surface for applying a variable ultrasonic force onto the surface and a means is provided for monitoring the position of the particles with respect to the surface, particularly as the intensity of the ultrasonic force is varied, so that the intensity level at which the complex breaks can be noted. In an alternative embodiment, the surface can include spatially addressable subregions, with each subregion having a different surface-bound binding member attached thereto. This embodiment of the device can be used to measure the binding forces of a plurality of different surface-bound binding members. In another alternative embodiment the binding forces of a plurality of different particle-bound binding members may be measured by attaching each type of binding member to a different distinguishable class of particle.

Brief Summary Text (25):
It has also been discovered that ultrasonic force can be used in a binding assay to dislodge and remove labeled compounds that adhere nonspecifically to a surface or that become bound due to cross-reactivity with an analog of an analyte. By the dislodging and removal of labeled compounds that are not bound by specific binding reactions, false positive results can be greatly reduced and the sensitivity of a binding assay can be improved.

Brief Summary Text (26):
Therefore, according to another aspect, the present invention is an assay device and method for detecting the presence or amount of an analyte in a test sample. In this embodiment, a surface is provided that has immobilized binding members that bind specifically to an analyte attached thereto, a reaction vessel for exposing the surface to the test sample, and a labeled reagent that, when contained in the test sample and exposed to the surface, becomes immobilized with respect to the surface specific ally in relation to the amount of the analyte in the test sample. An ultrasonic force means is operatively disposed with respect to the surface for applying an ultrasonic force onto the surface for dislodging any of the labeled reagent that binds non-specifically to the surface or that becomes immobilized on the surface of the surface due to cross-reactivity with an analog of the analyte, and a means is provided for detecting the amount of labeled reagent that remains immobilized with respect to the surface after the ultrasonic force is applied. In one embodiment, the labeled reagent of the assay device is in the form of a plurality of particles that have second binding members attached thereto, wherein the second binding members are capable of undergoing a selective binding interaction in relation to the amount of the analyte in the test sample, and the assay device includes a means to observe the particles during and after the application of the ultrasonic force. In an alternative embodiment, the surface can include spatially addressable subregions, with each subregion having a different surface-bound binding member attached thereto so that a plurality of analytes can be detected simultaneously in one assay.

Brief Summary Text (27):
It has also been discovered that ultrasonic force may be used in a "two-bead" assay, (that is, an assay

using binding interactions between two or more types of particles to determine the presence or absence of an analyte). In this embodiment, ultrasonic force is used to dislodge particles that bind to each other by nonspecific binding.

Drawing Description Text (2):
FIG. 1 is a schematic view of an assay device of the present invention having a transmission of ultrasound through an assay cell wall.

Drawing Description Text (3):
FIG. 2 is a schematic view of an assay device of the present invention having an ultrasound source immersed directly in an liquid medium of an assay cell.

Detailed Description Text (8):
The requirement that the surface and the particles have binding members attached to them is met by any covalent or non-covalent form of attachment of the binding members to the surface and the particles, either directly or through any type of linking group. The binding members should be bound to the surface and to the particles strongly enough so they are not displaced by the application on the ultrasonic force during the practice of the method of the present invention

Detailed Description Text (10):
The term "reaction vessel" refers to any type of receptacle or holder that provides a way for the surface to be exposed to the particles. Typically, the surface will be submersed in a liquid medium and will be exposed to particles suspended in the liquid medium. The reaction vessel, therefore, is preferably of a shape that allow it to retain a liquid medium. For example, a typical microtiter well or assay cell can be used as the reaction vessel. In one device configuration, ultrasound is transduced through one or more of the reaction vessel walls. In this case, the thickness of the walls, their material of construction and geometry must be optimized to transmit sound. In a second device configuration, ultrasound is generated in the solution of the reaction vessel, and in this case the reaction vessel must be constructed to reflect sound. The general principles of vessel design are outlined below.

Detailed Description Text (11):
The term "ultrasonic force" refers to any acceleration force applied by means of a longitudinal or transverse pressure wave arising from an ultrasonic source, such as an ultrasonic transducer. The terms "ultrasonic force means", "ultrasonic power source" and "ultrasonic sound source" all refer interchangeably to any apparatus, such as an ultrasonic transducer, that is capable of imparting an ultrasonic force. Preferably, the ultrasonic force means is an ultrasonic piezo electromechanical transducer. The term "variable force" refers to an ultrasonic force that can be controlled and varied, particularly across a range of intensities from a force that is too weak to separate binding member complexes to a force that is strong enough to separate binding member complexes. Preferably, the amplitude, frequency, pulse rate, pulse duration, and wave-form of the ultrasonic force are all selectable and controllable so that the force delivered to the binding member complexes can be fine-tuned and ramped. In a typical ultrasonic piezo transducer, these variables can be controlled by controlling the voltage input to the transducer through an external function generator and power amplifier.

Detailed Description Text (12):
The terms "operatively disposed" or "operatively coupled", when used herein to describe the relationship between the surface and the ultrasonic force means, refers to any method of coupling a source of ultrasonic force to the reaction vessel or to a medium contained in a reaction vessel so that ultrasonic force is delivered to the surface and the particles.

Detailed Description Text (13):
The phrase "means for monitoring the position of the particles with respect to the surface", as used herein, refers to any means of determining whether particles are immobilized on the surface, thereby indicating whether there is sufficient binding affinity between surface-bound binding members and particle-bound binding members to form complexes, and whether any immobilized particles are moved off of or around the surface by the application of the ultrasonic force, thereby indicating whether the applied force was strong enough to separate the complexes. Preferably, the monitoring is done by

optical microscopy. This can be achieved by simply positioning a microscope so that the surface and any particles immobilized thereon can be observed. Preferably, the position-monitoring is automated by providing, for example, a digital image acquisition system and processing system for recording digital images of the surface and for identifying and counting particles that are immobilized thereon. Other possible means of monitoring the presence and position of particles on the surface include, for example, fluorescent detection, color detection, electrochemical detection, magnetic detection measurement of weight differences, and chemical detection, such as detection of enzymatic reactions.

Detailed Description Text (19):
In this embodiment of the invention, it is not necessary that the labeled reagent be a particle, as defined above, or that the labeled reagent bind directly to the surface. All that is necessary is that the assay involves some type of binding event that causes the labeled reagent to become immobilized with respect to the surface in some detectable or identifiable manner, that this immobilization can be correlated either directly or indirectly with the amount of analyte in the test sample and that there is a potential for false positive results in the assay due to binding events that are not correlated with the amount of analyte in the test sample. According to this aspect of the invention, ultrasonic force is used to separate and remove non-specifically bound labeled reagent.

Detailed Description Text (20):
In a binding assay according to the present invention, excess analyte or nonspecifically bound particles that are dislodged by the application of ultrasonic force are removed from the assay surface. To accomplish this, the ultrasonic force may be used in conjunction with additional forces such as, for example, magnetic force, optical force, electrostatic force, hydrodynamic force, gravitational force or combinations thereof

Detailed Description Text (22):
The devices of the present invention are illustrated schematically in FIGS. 1 and 2, which depict two alternative preferred means by which an ultrasonic transducer may be operatively disposed with respect to the surface for applying a variable force on the particles. Of course, the present invention is not limited to these two alternatives, and any means for coupling an ultrasonic source to apply an ultrasonic force to the surface may be used.

Detailed Description Text (23):
In FIG. 1, a reaction vessel 10 includes a bottom surface 12 having surface-bound binding members 14. The reaction vessel 10 includes a liquid medium 20. A plurality of particles 16 have particle-bound binding members 18 that have an affinity for the surface-bound binding members, so that complexes 19 are formed between the surface-bound binding, members and the particle-bound binding members. An ultrasonic sound source 24 is positioned so that ultrasound is transmitted through a conduction medium 25, such as water, and through the bottom surface of the assay cell to impart a force (represented by arrow 26) onto the particles. A microscope 30 is positioned so that movement of the particles can be monitored.

Detailed Description Text (24):
In FIG. 2, a reaction vessel 10' includes a bottom surface 12' having surface-bound binding members 14'. In this embodiment, the bottom surface 12' is made of a transparent material. The reaction vessel 10' includes a liquid medium 20'. A plurality of particles 16' have particle-bound binding members 18' that have an affinity for the surface-bound binding members, so that complexes 19' are formed between the surface-bound binding members and the particle-bound binding members. An ultrasonic sound source 24' is positioned so that it is submersed in the liquid medium of the reaction vessel so that ultrasound is transmitted into the liquid medium of the reaction vessel to impart a force (represented by arrow 14') onto the particles. A microscope 30' is positioned so that movement of the particles can be monitored through the transparent bottom surface 12'.

Detailed Description Text (25):
As explained below, it is easiest to understand how the force is applied to the beads in the force configuration depicted in FIG. 1. However, the efficiency in transmitting an ultrasonic force to the particles is severely attenuated by the reaction vessel wall in the first configuration and thus the

configuration in FIG. 2 is preferred.

Detailed Description Text (28):
Either the configuration of FIG. 1 or the configuration of FIG. 2 may be used in the methods of the present invention. The procedure for using a device of the present invention to characterize binding forces is to contact the particles with the surface so that if the particle-bound binding members have a binding affinity for the surface-bound binding members, complexes are formed and particles become immobilized on the surface. Preferably, the surface and the particles are submerged in a liquid medium during the steps of this process. The presence of the particles immobilized on the surface may be monitored by, for example, observing them by optical microscopy. An ultrasonic force is then applied to the particles and any resulting change in the position of the particles and, in particular, in the number of particles that remain immobilized on the surface, is noted. Preferably, the ultrasonic force is applied at an intensity that is too weak to have any effect on any of the particles and is increased gradually or in stages until it is sufficient to completely rupture all complexes and cause all the particles to become mobile. The number of immobilized particles can be counted at each stage and plotted as a function of the amount of force that is applied. Alternatively, a force of a given intensity can be applied and held and the behavior of particles as a function of time in response to the applied force can be observed and recorded.

Detailed Description Text (29):
The ultrasonic force can be applied in conjunction with other forces such as magnetic force, optical force, hydrodynamic force, gravitational force and combinations thereof. These additional forces are helpful in applying force to a particle over a wide range of time and removing dislodged particles from the field of view of the experiment.

Detailed Description Text (30):
The procedure can be repeated to generate sets of data regarding particular ligands and receptors. The procedure for simultaneously characterizing the binding forces of a plurality of surface-bound binding members with a particle-bound binding member is essentially the same, except that in the step of monitoring or observing the particles that are immobilized on the surface, the spatial location of the particles is noted, so that is can be determined which subregions have particles attached to them and which subregions do not have particles attached to them at any given level or ultrasonic force. In this way, the relative binding strength of different surface-bound binding members can be determined.

Detailed Description Text (31):
The procedure for simultaneously characterizing the binding forces of a surface-bound binding member with a plurality of different particle-bound binding members is essentially the same, except that in the step of monitoring or observing the particles that are immobilized on the surface, the classification of the particles (for example, the size of the particle) is noted, so that is can be determined which class of particle remains attached to the surface and which class of particle does not remain attached to the surface at any given level or ultrasonic force. In this way, the relative binding strength of different particles-bound binding members can be determined.

Detailed Description Text (32):
The present invention also includes methods of conducting assays to determine the presence of an analyte in a test sample. Again, either the configuration of FIG. 1 or FIG. 2 may be used. In assays to determine the presence of an analyte, the ultrasonic force that is applied is selected so that it is sufficiently strong to dislodge any of the labeled reagent or particles that bind non-specifically to the surface or that becomes immobilized on the surface due to cross-reactivity with an analog of the analyte and is not strong enough to dislodge labeled reagent or particles that are immobilized on the surface due to specific binding. In other words, ultrasonic force is used to decrease the background from -an assay and thereby increase the accuracy of the assay. The appropriate amount of ultrasonic force to be is applied will vary according to the particulars of a given assay and can be readily determined by conducting a few test runs before an assay is used in practice for diagnostic purposes or for environmental sensing. The ultrasonic force can be applied in conjunction with other forces such as magnetic force, optical force, hydrodynamic force, gravitational force and combinations thereof to remove dislodged labeled reagent or particles from the assay device. The assay device and methods can

be readily modified for conducting simultaneous assays for the identification of multiple analytes in a single assay by providing patterned surfaces and different binding members on different classes of beads.

Detailed Description Text (34):
CONSIDERATIONS FOR SELECTING OR MODIFYING THE ULTRASONIC FORCE

Detailed Description Text (35):
The following discussion relates to considerations to be taken in to account in modifying an ultrasonic sound source for use in the present invention.

Detailed Description Text (36):
The exact force that can be exerted on a binding complex depends on several controllable variables, including the intensity and character of the ultrasound source, the shape, size and composition of the cell or vessel in which the assay is performed and the type of interface between the ultrasound source and the cell.

Detailed Description Text (40):
Typical commercial power ultrasonic transducers operate at 20 kHz with an intensity of 1 W/cm.sup.2 of power. The acceleration amplitude (a.sub.o) of the sound waves generated by such transducers is 15,800 m/s.sup.2. Either increasing the frequency of the transducer to 40 kHz or the intensity to 4 W/cm.sup.2 will produce 1,000 pN forces, which is significantly larger than the forces that have been measured between some of the strongest ligand -receptor pairs.

Detailed Description Text (41):
Typical commercial 20 kHz ultrasound transducers used for cleaning purposes are optimized to produce vigorous cavitation and heating and thus should be modified to be useful in the methods of the present invention. In the methods of the present invention, cavitation and heating are undesirable because the forces of cavitation and effects of heating could destroy or rupture any binding complexes indiscriminately and could cause binding members to become detached from the surface and from the particles. Cavitation in a medium exposed to ultrasound is caused by the formation of gas bubbles. Cavitation can be avoided by increasing the frequency of the ultrasound or by using pulsed sound waves. At frequencies beyond 20 kHz, cavitation decreases because gas bubbles do not have time to form. To minimize cavitation and to provide a more controllable force for force differentiation purposes, frequencies in the range of 80 kHz -10 MHz are optimal. Cavitation can also be avoided by using pulsed sound waves. It has been found that when ultrasound is introduced into a medium, there is a delay between the introduction of sonic energy and the onset of cavitation. For example, a 20 kHz wave requires a pulse of at least 20 msec to produce cavitation: Therefore, cavitation can be avoided by using pulsed waves with pulses of less than 20 msec.

Detailed Description Text (42):
Another modification that can be made to conventional ultrasound generating systems to improve their usefulness in the methods of the present invention is to alter the waveform to a triangle or sawtooth waveform. Typical conventional ultrasound generating systems produce a sine or square waveform. In the methods of the present invention, these wave-forms will cause the particles to move towards and away from the surface at equal forces. Acceleration of particles toward the surface is undesirable because it will lead to increased loading forces, increased areas of contact and increased adhesion. A saw tooth or triangular waveform that is designed to rapidly accelerate the particles away from the surface and slowly accelerate the particles towards the surface is preferable.

Detailed Description Text (43):
Another consideration to be taken into account in designing a device according to the present invention is the manner in which the ultrasonic force is transmitted to the surface. As described above, an ultrasonic force generator may be positioned so that ultrasonic force is transmitted through the bottom of the reaction vessel (FIG. 1) or it may be immersed in a liquid medium in the reaction vessel so that the ultrasonic force is transmitted directly through the liquid medium to the surface. The efficiency of the transmission of a longitudinal pressure wave from one medium into another is determined by the

acoustic impedance (R) of the medium which is equal to the product of the density and speed of sound in the medium. The acoustic impedance of several materials are presented in Table 1.

Detailed Description Text (45):
Note that the pressure can actually increase as the sound passes from one phase to another while the intensity actually decreases and that a longitudinal wave is transduced more efficiently from a low-to-high impedance material than from a high-to-low impedance material. This means that the highest sound intensities will be produced when a metal ultrasonic horn is immersed in the liquid of the cell (FIG. 2). However, by choosing materials carefully and including a liquid conduction medium the transmission of ultrasonic power across two solid interfaces can be achieved will as little as 50% attenuation. The fact that sound can be transmitted across solid surfaces suggests that the configuration shown is FIG. 1 may be used, but two additional consideration must be taken into account. First, the intensity of sound in a solid decays exponentially into a solid, and the decay factor is inversely related to the square of the frequency of sound. The decay of sound suggests that the walls of the cell should be made as thin as possible to avoid undesirable levels of attenuation. Second, solids can support transverse waves and these waves manifest themselves at liquid-solid interfaces. Transverse acoustic waves take on at least three different forms: surface acoustic waves, Lambs waves and Love waves. These transverse waves produce lateral displacement and acceleration at the surface which can produce torque on the beads and amplifies the force delivered to the ligand-receptor interaction. The result is that secondary lateral effects can have strong effects and can lead to inhomogeneous force transduction across a surface.

Detailed Description Text (50):
The ability of ultrasound to displace micron scale beads was tested with several types of beads, several cell configurations and several ultrasonic power configurations. The position of the beads was determined with an optical microscope.

Detailed Description Text (52):
i. Ultrasound: Model 250 sonic disrupter, Bransonic ultrasonics. This is a 250 W, 20 kH ultrasonic source with microtip horn. The commercial power supply can produce up to 200 microns of tip displacement but we by-passed this source and used a 0-10 V peak-to-peak signal with a function generator. This level of power is much less than is supplied with the lowest level of the commercial power supply.

Detailed Description Text (56):
The beads were added to the wells in PBS buffer and allowed to sit for approximately one hour. From previous experience, we know that under these conditions the beads adhere to the surface so strongly that they can not be removed using the magnetic force generated by strong permanent magnets. All the beads were violently displaced from the surface in both the microtiter well and microscope slide cells when the microtip of the ultrasound was placed in direct contact with the solution (as in FIG. 2).

Detailed Description Text (57):
The beads could not be displaced from either cell when microtip was placed beneath the well in a transmission mode (FIG. 1). The difference in behavior is attributed to the severe attenuation of the ultrasound when it is transmitted through the thick walls of the microtiter well or microscope slide. To overcome this limitation, a cell was constructed from a 1/4" diameter well machined in an aluminum plate with a 70 micron thick plastic bottom. When the tip of the ultrasound was placed in direct contact with the plastic bottom the beads were displaced at voltages between 5-10 Vpp. It is important to note that the initiation of the displacement of the beads took place at a critical voltage, thereby demonstrating force differentiation. This voltage differed from well to well and across a field of view in any given well. We attribute the well to well variation in force transduction to differences in mechanical transduction efficiency resulting from variations in loading and positioning.

Detailed Description Text (58):
The first beads that were displaced in a well were those directly under the ultrasonic source. However, beads were displaced at different levels of sound across the plastic membrane. In some places the beads were completely displaced while in others no beads were displaced. This behavior suggests that ultrasound excited standing waves in the plastic bottom. In fact, beads that were displaced were

observed to travel across the surface of the cell and concentrate at specific points. This mode of force transduction produces complex force trajectories across the well but can be used to determine the intermolecular force if it can be referenced to other specific intermolecular interactions.

Detailed Description Text (62):
The capacity of ultrasound to identify specific molecular interactions was demonstrated using streptavidin-biotin. This interaction is among the strongest occurring in nature.

Detailed Description Text (63):
The capacity of ultrasound to displace specifically bound beads was tested with Seradyne beads functionalized with streptavidin and biotin through a monolayer of polymeric polyethylene glycol (See, for example, U.S. patent application Ser. No. 09/008,782, filed Jan. 20, 1998 by the same inventor and having the same assignee. This application is incorporated herein by reference). The cell was also functionalized with biotin using a PEG coating. The polymeric coating was used to minimize nonspecific forces.

Detailed Description Text (64):
Ultrasound was delivered through the bottom of the aluminium/plastic wells and the position of the beads was monitored with the Axiotech microscope. The ultrasound almost totally displaced the biotin beads which migrated to a node on the surface. The streptavidin beads were not displaced by the ultrasound up to a 10 Vpp power level. This power level was always observed to displaced unfunctionalized beads.

Current US Cross Reference Classification (1):
134/1

Current US Cross Reference Classification (2):
134/184

Other Reference Publication (1):
Haga et al, "Effect of Ultrasonic Irradiation on the Dissociation of Antigen-Antibody Complexes. Application to Homogeneous Enzyme Immunoassay", Chem. Pharm. Bull. 35(9) (1987), pp 3822-2830).

Other Reference Publication (2):
Chen et al, "Ultrasound-Accelerated Immunoassay as Exemplified by Enzyme Immunoassay of Choriogonadotropin", Clinical Chemistry, 30, (1984), pp 1446-1451.

Other Reference Publication (4):
Thomas et al, Measurement of Antigen Concentration by an Ultrasound-Enhanced Latex Immunoagglutination Assay, Ultrasound in Med. & Bio, vol. 22, No. 9, (1996), pp. 1277-1284.

CLAIMS:

1. An assay device for detecting the presence or amount of an analyte in a test sample, the assay device comprising

a surface that has binding members that bind specifically to an analyte attached thereto,

means for exposing the surface to the test sample,

a labeled reagent that, when exposed to a surface that has been exposed to the test sample, becomes immobilized with respect to the surface specifically in relation to the amount of the analyte in the test sample,

ultrasonic force means operatively disposed with respect to the surface for applying an ultrasonic force onto the surface for dislodging any of the labeled reagent that binds non-specifically to the surface or that becomes immobilized on the surface due to cross-reactivity with an analog of the analyte, and

means for detecting the amount of labeled reagent that is immobilized with respect to the surface.

2. The assay device of claim 1 the ultrasonic force means is an ultrasonic transducer capable of applying a pulsed ultrasonic force, and wherein the amplitude, frequency, pulse duration and/or wave-form of the ultrasonic force are selectable so that the ultrasonic force is sufficient to remove from the surface any of the labeled reagent that binds non-specifically to the surface or that cross-reacts with the an analog of the analyte, and so that the ultrasonic force is insufficient to remove any analyte that binds to the binding member and any labeled reagent that becomes immobilized on the surface in relation to the amount of analyte.

3. An assay device for detecting the presence or amount of an analyte in a test sample, the assay device comprising

a surface that has first binding members that bind specifically to an analyte attached thereto,

means for exposing the surface to the test sample,

a plurality of particles that have second binding members attached thereto, wherein the second binding members are capable of undergoing a selective binding interaction whereby the particles, when exposed to the surface that has been exposed to the test sample, become immobilized specifically with respect to the surface in relation to the amount of the analyte in the test sample,

ultrasonic force means operatively disposed with respect to the surface for applying an ultrasonic force onto the surface for dislodging any of the particles that bind non-specifically to the surface or that become immobilized on the surface due to cross-reactivity of the second binding member with an analog of the analyte, and

means for monitoring the position of the particles with respect to the surface which detects the presence or amount of analyte in the test sample.

9. An assay device for simultaneously detecting the presence or amount of a plurality of different analytes in a test sample, the assay device comprising

a surface that has spatially distinguishable subregions, wherein each subregion has a different surface-bound binding members attached thereto, wherein each different surface-bound binding member binds specifically to a different analyte,

means for exposing the surface to the test sample,

a plurality of sets of particles that have particle-bound binding members attached thereto, wherein the particle-bound binding members are capable of undergoing a selective binding interaction whereby the particles, when exposed to the surface that has been exposed to the test sample, become immobilized specifically with respect to the surface in relation to the amount of an analyte in the test sample, and wherein each set of particles is selective of a different analyte,

ultrasonic-force means operatively disposed with respect to the surface for applying an ultrasonic force onto the surface for dislodging any of the particles that bind non-specifically to the surface or that become immobilized on the surface due to cross-reactivity of a particle-bound binding member with an analog of an analyte, and

means for monitoring the position of the particles with respect to the subregions of the surface which detects the presence or amount of the plurality of different analytes in the test sample.

10. An assay device for detecting the presence or amount of an analyte in a test sample, the assay device comprising

a plurality of first particles that have first binding members that bind specifically to an analyte attached thereto,

a reaction vessel that includes means for exposing the plurality of first particles to the test sample,

a plurality of second particles that have second binding members attached thereto, wherein the second binding members are capable of undergoing a selective binding interaction whereby the second particles, when exposed to first particles that have been exposed to the test sample, bind to the first particles in relation to the amount of the analyte in the test sample and form an aggregate,

ultrasonic force means operatively disposed for applying an ultrasonic force to the reaction vessel for dislodging any of the analyte or second particles that bind non-specifically to the first particles or that bind to the first particles due to cross-reactivity of the second binding member with an analog of the analyte, and

means for determining the presence or absence of aggregates which detects the presence or amount of analyte in a test sample.

WEST

Generate Collection | Print

L15: Entry 15 of 66 File: USPT Jun 15, 1999

DOCUMENT-IDENTIFIER: US 5911837 A
TITLE: Process for treatment of semiconductor wafers in a fluid

Detailed Description Text (33):
The structure of tank 13 also provides advantages when using megasonic transducers. Tank 13 may have one or more megasonic transducers 2 mounted thereon for agitation of the solution. The transducers are preferably oriented between perpendicular and 30.degree. off perpendicular to the gas stream with the wafers oriented parallel to the megasonic beam.

Detailed Description Text (34):
The megasonics in a preferred embodiment are mounted on the side of the tank with the longer taper. Opposite this side is a shorter tapered side. The sides are tapered to accomplish two functions. The first is to insure the megasonic power does not reflect off the far wall and return to the transducers. Such reflected energy would result in burning up the transducers and thereby lead to a short component lifetime. The second reason for the choice of the tapered walls is to pass the megasonic power through the zone where the volume of silicon wafers is to be processed and use the reflected beam off the far wall to make a second pass through the zone of silicon wafers. In doing so, each megasonic pulse has two passes through the wafers to increase the particle removal efficiency.

Detailed Description Text (39):
For the sulfuric acid process, acid enters a tank through a delivery tube in the weir, so that the acid goes to filtration first before entering the process area of the tank. Delivery of acid from a recirculating unit is through the bottom of the tank. After wafers with photoresist are introduced to the process area of the tank, ozone is diffused into the tank while megasonic transducers are activated. The other configuration of the sulfuric acid clean using ozone is to diffuse ozone (O.sub.3) into the tank through the diffuser with the resisted wafers present, then activate the UV light. The UV light will generate the oxygen free radical to react directly with the organic matter on the silicon wafers and to act as an oxidant which reacts with the sulfuric acid to form the traditional Caro's Acid which reacts with the photoresist. This reaction is simultaneous with the sonic energy of the dual frequency transducers.

Detailed Description Text (40):
For the RCA clean, the tank operates in overflow mode. Deionized water cascades continuously at a variable flow rate (0.5, 1, 5 and 10 gpm), or the tank is in static mode. The wafers are first rinsed, then the water cascade is turned off. Ozonated water is generated in the tank and/or is pumped into the tank and then the ammonia gas (NH.sub.3) is diffused into the tank to create the SC1 solution. Optionally, ozone in conjunction with UV radiation may be used to generate the oxygen free radical. The megasonic transducers are activated, operating in dual frequency mode and firing alternately in order to prevent overheating of the crystals. After processing, the water cascade is turned on to flush (from the bottom of the tank) the SC1 solution from the tank. The water flush/rinse is timed and the drain may also have a resistivity monitor in-line. When the tank and wafers are rinsed, the water line switches to hot deionized water to elevate the temperature in the process tank. When the tank temperature reaches 70.degree. C., the overflow is turned off and the tank returns to static mode. Ozone gas is then diffused into the tank, followed by hydrochloric gas, to create the SC2 solution. Optionally, ozone in conjunction with UV radiation may be used to generate the oxygen free radical. The megasonic transducers are activated.

After processing, the water cascade is turned on to flush the tank and rinse the wafers based on time and resistivity. A final rinse is performed with hot deionized water based on time.

Current US Original Classification (1):
134/2

Current US Cross Reference Classification (1):
134/25.4

Current US Cross Reference Classification (2):
134/26

Current US Cross Reference Classification (3):
134/30

Current US Cross Reference Classification (4):
134/31

Current US Cross Reference Classification (5):
134/37

Current US Cross Reference Classification (6):
134/902

WEST

End of Result Set

Generate Collection | Print

L5: Entry 1 of 1 File: USPT Jun 21, 1983

US-PAT-NO: 4389071
DOCUMENT-IDENTIFIER: US 4389071 A

TITLE: Enhancing liquid jet erosion

DATE-ISSUED: June 21, 1983

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson, Jr.; Virgil E.	Gaithersburg	MD		
Lindenmuth; William T.	Columbia	MD		

US-CL-CURRENT: 299/14; 134/1, 175/67, 239/380, 299/17

ABSTRACT:

Process and apparatus for enhancing the erosive intensity of a high velocity liquid jet when the jet is impacted against a surface for cutting, cleaning, drilling or otherwise acting on the surface. A preferred method comprises the steps of forming a high velocity liquid jet, oscillating the velocity of the jet at a preferred Strouhal number, and impinging the pulsed jet against a solid surface to be eroded. Typically the liquid jet is pulsed by oscillating the velocity of the jet mechanically or by hydrodynamic and acoustic interactions. The invention may be applied to enhance cavitation erosion in a cavitating liquid jet, or to modulate the velocity of a liquid jet exiting in a gas, causing it to form into discrete slugs, thereby producing an intermittent percussive effect.

17 Claims, 28 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 11